# SUMMARY MINUTES

# OF THE

# GASTROENTEROLOGY AND UROLOGY DEVICES

# ADVISORY PANEL MEETING

# OPEN SESSION

**August 17, 2001**

**Conference Room 020B**
**9200 Corporate Blvd.**
**Rockville, Maryland**

**Gastroenterology and Urology Devices**
**Advisory Panel**

**August 17, 2001**

**Panel Participants**

Anthony N. Kalloo, M.D.
Panel Chair
Gastroenterologist
The Johns Hopkins Hospital

Mary Gellens, M.D.
Voting Member
Nephrologist
St. Louis University Hospital

Arthur D. Smith, M.D.
Voting Member
Urologist
Albert Einstein College of Medicine

Joseph H. Steinbach, Ph.D.
Voting Member
Biomathematician
V.A. Medical Center

Karen L. Woods, M.D.
Voting Member
Gastroenterologist
Baylor College of Medicine

Diane K. Newman, RNC, MSN, CRNP, FAAN
Consumer Representative
PENN Center for Continence and Pelvic Floor Disorders
University of Pennsylvania

Michael S. Banik
Industry Representative
Boston Scientific

Michael S. Epstein, M.D.
Temporary Voting Member
Gastroenterologist
Digestive Disorders Associates

Walter Koltun, M.D.
Temporary Voting Member
Colorectal Surgeon
Hershey Medical Center

Stephen McClane, M.D.
Temporary Voting Member
Colorectal Surgeon
The Stamford Hospital

Mark A. Talamini, M.D.
Temporary Voting Member
Surgeon
The Johns Hopkins University School of Medicine

**FDA Participants**

Jeffrey W. Cooper, D.V.M.
Executive Secretary, Gastroenterology and Urology Devices Panel

Nancy Brogdon
Director, Division of Reproductive, Abdominal, and Radiological Devices

Aron Yustein, M.D.
Clinical and Lead Reviewer for PMA P010020

Kathleen Olvey
Preclinical Reviewer for PMA P010020

**Sponsor Participants**

Larry Getlin
Vice President for Regulatory, Medical Affairs, and Quality Systems (AMS)

David Worrell
Senior Regulatory Affairs Specialist (AMS)

Dr. W. Douglas Wong, Investigator
Memorial Sloan Kettering Cancer Center

Dr. Susan Congilosi, Investigator
Colon and Rectal Surgery Associates, St. Paul, Minnesota

**OPEN SESSION**

**Panel Chair Anthony N. Kalloo, M.D.,** called the session to order at 9:42 a.m., noting that the voting members present constituted a quorum.

**Panel Executive Secretary Jeffrey W. Cooper, D.V.M.,** read appointments to temporary voting status for Michael S. Epstein, M.D., Walter Koltun, M.D., Steven McClane, M.D., Mark A. Talamini, M.D., and Lawrence W. Way, M.D. (not present). Dr. Cooper also read the conflict of interest statement, noting that Arthur D. Smith, M.D., had declared an interest in a matter deemed unrelated to the discussion at hand and his full participation was permitted. Dr. Cooper listed tentative future panel meeting dates as February 1, May 27, August 9, and November 7, 2002.

**OPEN PUBLIC HEARING**

**Dr. Cooper** noted that one written statement had been received for the Open Public Hearing: a letter from the National Association for Continence requesting the panel to consider recommending approval of the device to be discussed, an artificial bowel sphincter.

**Nancy B. Loitz, a recipient of the device,** read a statement to the panel in which she discussed her positive, life-changing experience with the device and expressed hope that it would be made available to others.

**Dr. Cooper** introduced **Nancy Brogdon, Director of the Division of Abdominal and Radiological Devices,** and asked the rest of the panel members to introduce themselves and state their areas of expertise.

**OPEN COMMITTEE DISCUSSION--PREMARKET APPROVAL APPLICATION P010020 FOR AMERICAN MEDICAL SYSTEMS, INC.'S ACTICON NEOSPHINCTER**

**Sponsor Presentation**

**Larry Getlin, Vice President for Regulatory, Medical Affairs, and Quality Systems for American Medical Systems (AMS),** introduced the sponsor presentation, stating that the device was essentially the same as the AMS Sphincter 800, a device previously approved under a Humanitarian Device Exemption (HDE) that has some 20 years of clinical use.

**David Worrell, Senior Regulatory Affairs Specialist for AMS,** discussed the problem of severe fecal incontinence and read the proposed indication for use for the device. He explained the recent device history and the modifications made to address fecal incontinence.

**W. Douglas Wong, M.D., study investigator,** presented effectiveness results of the prospective, nonrandomized multicenter study, in which subjects served as their own control. He discussed study enrollment, patient demographics, inclusion and exclusion criteria, and etiology of fecal incontinence, noting that all patients had had conventional medical management and most had had surgical management but failed previous treatment. The primary effectiveness endpoint was the Fecal Incontinence Scoring System (FISS) at three and twelve months, with secondary endpoints of anal manometry, a health status questionnaire, and a fecal incontinence quality of life questionnaire. After explaining the FISS score definitions, Dr. Wong showed data that the device achieved a drop in the mean FISS score that was more than twice that needed for clinical success at

both six and twelve months and that twelve-month follow-up data showed the device achieved clinical success for the majority of patients with significantly improved continence. Scores on anorectal manometry showed a statistically significant change after device implantation, scores on the Health Status Questionnaire improved significantly, and the Fecal Incontinence Quality of Life Scale scores improved substantially.

**Dr. Susan Congilosi, study investigator,** presented safety results from the clinical study. She reported on 15 adverse events at implantation, which were resolved without long-term sequelae. Device-related adverse events were numerous but not unanticipated or life-threatening, with the majority being pain/discomfort, infection, or erosion. Dr. Congilosi presented statistics on surgical intervention for device-related adverse events, which occurred in 142 of the events, and on device revisions, which occurred primarily due to infection or erosion. She presented variables significant for risk of erosion or infection and described the antibiotic regimen used, as well as factors important for risk minimization such as patient counseling or bowel preparation. Dr. Congilosi concluded that safety results showed no life threatening adverse events, that adverse events are manageable and resolve without long-term sequelae, and that device revisions do not lead to serious long-term sequelae.

**Mr. Worrell** concluded that in assessing the risk/benefit ratio, it is important to note the significant improvements in fecal continence and in the patient's quality of life. Adverse events were non-life-threatening and manageable and resolved without long-term consequences. He concluded that these risks are outweighed by the benefits of improved fecal continence and greatly enhanced quality of life.

Questions from the panel included whether subgroup analysis showed that certain patients are more likely to respond to the device, either by severity of disease or etiology. There were also questions on patients with comorbid conditions and their outcomes, on diabetic patients, and on procedures for colonoscopy with the device. The panel also asked about data from European experiences and about whether there were differences in male versus female patient experience.

**FDA Presentation**

**Aron Yustein, M.D.,** introduced the FDA review team, read the proposed indication for use, and discussed the regulatory history of the device. He briefly explained the etiology of fecal incontinence and outlined methods of medical or surgical management of it.

**Kathleen Olvey** presented the preclinical testing results, which included materials safety testing, evaluation of device performance, and sterilization. Biocompatibility testing and extractives testing of both the raw materials and final product found no evidence of any significant health risks. Performance testing of all components showed reliability and strength to be adequate for the estimated life cycle of the device. She stated that the proposed sterilization protocol was adequate to assure device sterility.

**Dr. Yustein** discussed the U.S. prospective clinical trials, which included a feasibility study and a pivotal trial. The feasibility study used an earlier version of the device adapted for the AMS urinary sphincter in a seven-year multicenter study of 21 patients. Safety results showed a 57% adverse event rate; a 43% surgical revision rate, and a 24% explantation rate. Effectiveness rates over a range of 7-76 months showed a

64% complete continence rate and a further 18% solid continence rate. After the feasibility study, device modifications were made to the cuff and the pressure balloon.

After describing the design and objectives of the pivotal trial, Dr. Yustein listed inclusion and exclusion criteria and patient demographics for etiology of incontinence and previous treatment. He defined and explained the primary and secondary effectiveness endpoints, noting an average drop of 57 points in the mean matched FISS scores from pre-implant to 12 month follow-up and an 85.2% rate of successful outcome based on evaluable patients. However, an intent-to-treat analysis of FISS scores at 12 months done by the FDA showed the success rate to be 51.3%. Dr. Yustein stated that the secondary endpoint of anorectal manometry showed statistically significant improvement, as did the fecal incontinence quality of life questionnaire and some but not all of the scores on the health status questionnaire.

On safety results, Dr. Yustein showed that the rate of adverse events was 87%, with 50% of all implanted patients receiving at least one device revision. The most common adverse events were pain, infection, and erosion, with infection and erosion the most common indications for revision. Some 25% of the patients required revision for an infectious complication, with no significant differences in rates of infection among sites, gender, or length of operation. Thirty percent of patients underwent device explantation, with the majority due to infection and/or erosion. No unanticipated adverse events occurred during the study and no deaths occurred.

Dr. Yustein concluded that fecal incontinence is a common health issue that can have a major impact on a patient's quality of life, and that there are several treatment alternatives, both surgical and nonsurgical, each with its own risk/benefit profile. The

Acticon neosphincter has been studied under two IDEs in the United States with approximately 135 patients. An intent-to-treat analysis of those patients showed 51.3% had a clinically significant improvement in fecal incontinence one year after implantation as defined by the FISS score. However, 50% of patients implanted required at least one surgical revision within one year and approximately 30% of patients required total device explantation within one year. The majority of revisions and explantations were a result of infection and/or erosion.

**Panel Discussion**

**Lead panel reviewer Mark A. Talamini, M.D.,** congratulated both the sponsors and panel members for bringing up the critical issues in a field of great interest to surgeons but one that poses stubborn problems of treatment. He cast the issue in terms of risk/benefit ratios, saying that when the alternatives are as extreme as incontinence and stomas, the risks must be considered within that framework.

In response to a question on explantation and on patient dissatisfaction, sponsors provided additional information on permanent explantation versus reimplantation and noted that all those explanted had reasons other than dissatisfaction with the device for explantation, such as infection or erosion. They found no link between infection or erosion and age, gender, previous pregnancy, or comorbid conditions such as diabetes.

Panel discussion focused on the difficulty of measuring how much the quality of life has been improved by the procedure and the problem of comparing device effects when the patient serves as his own control. It was noted that a strong placebo effect may have affected the quality of life measurements, which is hard to quantify given the lack of comparison to patients with stomas or to patients explanted for device failure. Panel

members asked why data from European patients was not included, but it was noted that other protocols were followed and different reporting procedures used.

**Panel Discussion of FDA Questions**

1) *Please discuss the safety profile of this device overall as well as in relation to other treatments for fecal incontinence.*

The panel as a whole recognized that the study reflects a high complication rate, but with the exception of one member, was willing to accept the rate relative to the benefits for patients. The panel's concern about complications could be mitigated by labeling that delineates careful patient selection and surgeon training requirements.

2) *Please discuss the clinical significance of a 24-point score reduction on the Fecal Incontinence Scoring System (FISS).*

The consensus of the panel was that a 24-point reduction is significant using the FISS. This finding is concordant with other study measures and has statistical basis as well.

3) *Please discuss the clinical significance of the overall changes in the parameters contained in the two quality of life questionnaires used as secondary endpoints during the pivotal trial.*

The panel thought that the clinical significance of the quality of life data was not as powerful as other aspects of the study. Inherent weaknesses include the lack of a control group and the non-inclusion of failures. However, how the data do reflect and agree with other study findings is not without significance, in the panel's view.

4) *Please comment on the Intent to Treat (ITT) Analyses submitted by the sponsor and the FDA and also on the effectiveness of the device for the treatment of severe fecal incontinence when analyzed by this method.*

The ITT analyses did not appear to alter the panel's opinion of effectiveness. However, they did underscore the panel's concern about failure rates, which the panel wished to see addressed in labeling.

5) *Please identify whether there are any patient populations or subgroups that you feel would either clinically benefit more from the device or be at higher risk for adverse events from implantation.*

Based on the data in the PMA, the panel did not see any groups clearly identified as benefiting or at high risk from the device, but the panel thinks such groups probably do exist. More information on them should be made available as more implants are done.

6) *Please discuss whether the device should be labeled for use in post-pubescent patients under the age of 18.*

The panel was split evenly between those who would approve the device for post-pubescent patients under 18 and those who would restrict its use to those 18 and over.

7) *Please discuss whether patient labeling, as submitted, is adequate to accurately inform the user of the risks and potential benefits of using the device.*

The panel recommended that the labeling should be revised and should be the primary vehicle for outlining the indications for use; outcome data with numbers given for carefully defined success and failure; postoperative expectations; intent to treat analysis results; qualifications for physicians; and risks of infection, complication, and revision. It was urged that the patient receive the labeling several days before the operation.

8) *Please discuss whether the professional labeling is adequate to accurately inform the physician of the risks and benefits of using the device and if there are any additions that would be appropriate.*

The panel recommended that the professional labeling should indicate all updated data on performance success rates, high-risk groups, specified contraindications, and warnings, as well as information on any available training or certification.

9) *In addition to the intent to treat analysis, please discuss whether the results of the evaluable analysis should be included in the professional and/or patient labeling.*

The panel agreed that these results should be included in the labeling.

**OPEN PUBLIC HEARING**

There were no requests to address the panel.

**FDA CLOSING COMMENTS**

There were no remarks from FDA representatives.

**SPONSOR CLOSING COMMENTS**

There were no remarks from the sponsors.

**PANEL VOTE**

**Dr. Cooper** read the panel voting instructions and options. Dr. Talamini summarized the panel discussion as having covered the FDA issues and stated that the majority concluded the device is effective as defined with an understanding of the risks entailed and safe within the scientific definition of safety. Two major categories of outstanding issues were the labeling revisions and training for surgeons.

A motion was made and seconded to recommend the PMA as approvable with the following conditions:

1) A training program should be developed by the company and the FDA. This condition passed by a vote of seven to one.

2) Modified labeling should provide a template for informed consent to give the patient device information that would include tables of success and failure rates, that would clearly state this device is an alternative to a stoma, and that would address potential risk factors in the physician labeling. This condition passed by a vote of seven to one.
3) The device was approved for used in post-pubescent patients 18 and older, with post-pubescent patients under the age of 18 to be covered under the HDE. This condition passed by a vote of five to three, with two of those opposed to the condition stating that they thought post-pubescent patients under the age of 18 should be covered by the PMA rather than the HDE.
4) A postmarketing follow-up study should be done on patients already enrolled in the study who have reached the one-year mark. They should be followed for one more year. Also, a follow-up of those patients who were lost to follow-up at the one-year mark should be done. These data should be made a part of the labeling. This condition passed by a vote of six to two.

The motion to recommend the PMA as approvable subject to the specific four conditions described above carried by a vote of seven to one. The member who voted against the motion stated that she opposed the motion because she thought the device needed a longer observational period, with closer attention to patient selection and complications, to prove safety and efficacy.

Panel Chair Dr. A. Kalloo thanked the panel, the sponsors, and the FDA and adjourned the session at 3:35 p.m.

I certify that I attended the Open Session of the Gastroenterology and Urology Devices Advisory Panel Meeting on August 17, 2001, and that this summary accurately reflects what transpired.

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Jeffrey W. Cooper, D.V.M.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Anthony N. Kalloo, M.D.
Panel Chair

Summary minutes prepared by
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